REMARKS/ARGUMENTS

Claims 116-137 are pending in this application.

The subject matter of Claims 81, 85, 87, 91, and 104-110 are re-presented as new claims 116-135.

Claims 111-115 have been cancelled due to the imposed restriction. Applicant reserves his right to pursue such subject matter in a divisional application.

Support for the claims 116-137 is found in the original claims and the specification as originally filed, e.g., pages 7-8, page 17, pages 19-20, and the discussion of detecting two, three or more antigens by cocktailing the primary antibodies, on pages 9-11, and the paragraph bridging pages 7-8.

Further exemplary support is as follows:

Support for "wherein the method can be completed in not more than 2 to 2.5 hours" is found on page 5, 1st paragraph.

Support for Claims 117 and 127 is found on page 13, lines 8-9.

Support for Claims 124, 125, and 134 is found on page 5, line 10 and page 16, lines 12-13.

Support for Claims 116, 125, and 126 is found on page 13, lines 10-15.

Support for Claims 122 and 132 is found on page 6, 1st paragraph.

Support for 135-137 is found, e.g., on page 8 Proclin™ 950, which is 2-methyl-4-isothiazolin-3-one as a preservative (see, e.g., http://www.sigmaaldrich.com/Brands/Supelco_Home/Biocides/ProClin.html) .

No new matter is added.

The issues outlined under 35 USC 112, second paragraph are no longer applicable because (A) those claims have been cancelled; and (B) the noted criticisms are not present in the claims here. Withdrawal of the rejection is requested.

The rejection under 35 USC 112, first paragraph is no longer applicable as the noted claims have been cancelled. Further, simultaneous detection, while believed to be within what is described in the application, is no longer specified in the claims as presented here. The pH of a buffer is not provided. Specified pairs of antigens suitable for detecting, while described in the application, are not provided in the claims here.

As to the Examiner's criticism of the application not being able to apply more than two primary and/or secondary antibodies and then detect the antigen-antibody complexes so formed, attention is directed to the attached Rule 132 Declaration where Dr. Tacha discusses that not only does the specification describe doing so, there have been countless experiments performed where indeed that type of staining has been successfully performed (see ¶ 19).

Accordingly, withdrawal of the rejection is requested.

The rejection under 35 USC 103(a) based on van der Loos, the specification, Myers or Hasui is traversed.

While van der Loos generally discloses detecting two antigens simultaneously (starting at page 13) and immunoenzyme triple staining (Chapter 8, starting at page 63). The Meyers paper does discuss automated staining using at least two antibodies but based on page 109 and table 2 of Meyers the method used is a sequential application of the antibodies and not a simultaneous double-stain protocol, through a 137 step sequential protocol. Hasui is also relied upon to teach automated staining.

As discussed by Dr. Tacha in his attached Declaration:

van der Loos generally describes detecting two antigens (starting at page 13) and immunoenzyme triple staining (Chapter 8, starting at page 63). As cited in the communication of March 23, 2007, van der Loos also describes the use of polymer conjugates but those polymer conjugates are dextran polmer conjugates (referred to as DAKO Envision™) on pages 4 and 15. This, however, is not what has been defined in the claims nor what is currently defined in the claims. As is apparent in the claims, a secondary antibody is coupled to a poly (alkaline phosphatase (AP)) moiety and/or poly (horseradish peroxidase (HRP)) moiety. These poly (AP) and poly(HRP) are different from the Dextran based technology that van der Loos describes (see also page 12, lines 14-16 of the application, referencing the previously cited Shi et al paper).

That the art cited does not describe the poly(AP) nor suggests its use, at least on this basis alone the rejections cannot be sustained.

Indeed, using the very same protocols that are described by van der Loos, the ability to do simultaneous double stains is hampered and not conventional, even as of 2006. For example, DAKO, a company that is also in the business of immunohistochemistry, explains in a lab manual double stains (attached) to do sequential staining (referencing Van Der Loos) -see *Conclusion* section. Thus, van der Loos does not provide any indication as to how to successfully perform a simultaneous double stain in the way as is defined in the application and claims of the patent application.

The Meyers paper does discuss automated staining using at least two antibodies but based on page 109 and table 2 of Meyers the method used is a sequential application of the antibodies and not a simultaneous double-stain protocol, through a 137 step sequential protocol. Hasui also discusses automated staining protocols. Neither Meyers or Hasui

describe employing a secondary antibody is coupled to a poly (alkaline phosphatase (AP)) moiety and/or poly (horseradish peroxidase (HRP)) moiety.

Further, nothing in van der Loos, Meyers, and Hasui provides any indication as to how to perform a double stain in not more than 2 to 2.5 hours nor that a double stain could be performed in not more than 15 steps.

Still further, none of these publications describe a primary rabbit monoclonal antibody.

Although not cited in the communication of October 18, 2007, the Shi paper was cited before by the patent office in the communication of March 23, 2007. The Shi paper is also referenced in page 12, lines 14-16 of the application.

The Shi paper does describe the same poly-HRP conjugates as in the claims of this application. Of course, as previously recognized by the patent office, the Shi paper does not describe a multiple staining protocol nor how to achieve that. The discussion in Shi certainly noted the sensitivity increase and detection efficiency using such polymer conjugated antibodies and the possibility that these polymer conjugates could be useful in multiple staining protocols, what we achieved in terms of a dramatically reducing the amount of steps required, provide time savings, have vastly better sensitivity than had ever been reported before for multiple staining protocols and also providing the ability to perform automated immunoassays was not at all predictable from what is described by Shi, van der Loos or the other publications cited by the patent office.

Dr. Tacha provides a few exemplary experiments of the advantages of the methodology defined in the claims. The experiments and attached photographs (FIGs. 1-3) compare the type of HRP technology that Mason and Van der Loos would have used verses polymer-HRP technology as provided in the claims. The comparisons used the same

dilutions, reagents, and protocol except for the actual HRP conjugates. In short, what these data show is the vastly superior results obtained when employing the polyHRP compared to other conventional HRP, including those described by van der Loos and Mason.

The results for three different double staining protocols is provided in the Figures (1-3) with the conventional HRP on the left panel and the poly HRP in the right panel. As is quite apparent from these photographs, the results, our technology is far superior to a standard HRP technique.

It is further worthwhile noting that when comparing the photos----the only difference was the two detections. However, the old methodology as from the cited art received the "modern" benefit of the diluents which did not exist at the time. They also got the benefit of all other enhancements techniques that did not exist. The reality of the staining with the old HRP, would have been virtually no staining with the old technique.

The sensitivity of the method coupled with the reagents used, allows us to easily cocktail up to 4 antibodies without producing background staining and further extended to 5 or 6 antibodies with reduced background compared to what had been done before. Indeed, we have, on numerous occasions, performed experiments that show that the method works well simultaneous triple and quadruple staining (i.e., using 3 or 4 antibodies). Further, the manner in which the claimed method is performed enables one to perform a double stain in not more than 2 to 2.5 hours nor that a double stain could be performed in not more than 15 steps and particularly relevant for the clinical setting, in an automated system that provides fast, clean and very good results. None of the publications describe any of these nor how to achieve such results.

Dr. Tacha also states that what we have achieved as exemplified in the figures attached and described in the patent application simply could not have been predicted to work as well as it did based on what was known before the patent application was filed and,

particularly, in view of what is described in van der Loos, Myers, Hasui, Shi or the other materials cited by the patent office.

Further, van der Loos or the other cited references do not describe or suggest including Proclin™ 950 as a important component in stabilizing the antibody cocktails. This facilitated the stabilizing of the double stain detection. Proclin™300 was ineffective as it broke down in Tris buffers but Proclin™950 was found to be compatible and therefore helpful in stabilizing the antibody cocktails. That the cited art neither describes or suggests this, the claims and, particularly, Claims 135-137 cannot be considered obvious in view of the citations.

Accordingly, withdrawal of this rejection is requested.

The rejection under 35 USC 103(a) in view of the above citations further in view of U.S. patent no. 6,537,745 (Chien), U.S. patent no. 4,690,890 (Loor), U.S. patent no. 5,108,896 (Philo), U.S. patent no. 5,089,423 (Diamandis) and U.S. patent application 2002/0173053 (Damaj) is also not applicable to the claims because while it is true that these secondary references describe BSA and sodium azide among others does not compensate for the deficiencies of the primary citations of van der Loos, Myers and Hasui as discussed above.

That the art cited does not describe the poly(AP) nor suggests its use, at least on this basis alone the rejections cannot be sustained.

The art cited does not provide any indication as to how to successfully perform a simultaneous double stain in the way as is defined in the application and claims of the patent application.

That the art cited does not provide any indication as to how to perform a double stain in not more than 2 to 2.5 hours nor that a double stain could be performed in not more than 15 steps.

Still further, none of these publications describe a primary rabbit monoclonal antibody.

That the art cited provides no suggestion for the achievements as exemplified in the figures attached and described in the patent application.

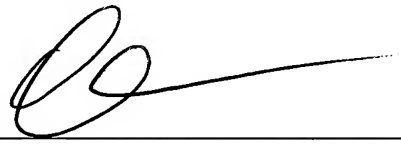
Further, van der Loos or the other cited references do not describe or suggest including Proclin™ 950 as a important component in stabilizing the antibody cocktails.

Withdrawal of this rejection is requested as well.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Daniel J. Pereira, Ph.D.
Registration No. 45,518

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 06/04)